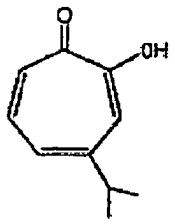
REMARKS

Claims 1, 3-19, 21-27 and 31-33 are pending.

Claims 1, 3-19, 21-27 and 31-33 have been rejected under 35 USC §103.

Before considering the Examiner's rejection under 35 USC § 103 in detail, Applicants wish to briefly summarize the key aspects of the present invention.

The present invention, as amended, relates to oral care compositions suitable for preventing or treating diseases or conditions of the oral cavity in warm-blooded animals including humans, comprising an oral care effective amount of an effective amount of a compound of Formula (I)



and at least one essential oil, and a pharmaceutically acceptable oral carrier.

Rejection Under 35 U.S.C. §103

Claims 1, 6-7, 17, 21 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 4,693,888 to Miyahara, et al. (Miyahara).

Applicants respectfully traverse this rejection.

Miyahara relates to caries-preventive composition comprises an antibody obtained by immunizing a mammal with at least one antigen selected from the group consisting of

Streptococcus mutans, its cell-wall fraction, fibrous substance fraction, glucosyltransferase fraction and protein antigen fraction, and a synergist selected from the group consisting of fluorine compounds, chlorhexidine and its salts, lytic enzymes, bacteriocins, glucosyltransferase inhibitors, proteases and dextranases. To this mixture, Miyahara further teaches optionally incorporating, inter alia, hinokitiol.

In contrast, the compositions of the present invention specifically require combining hinokitiol with an oral care effective amount of at least one essential oil in an oral carrier comprising about 20% to about 30% by weight of ethanol for preventing, eliminating or suppressing plaque, gum disease and oral malodor.

However, nowhere does Miyahara teach such oral care benefits for hinokitiol apart from its claimed antigen-synergist combination, much less improving such benefits of hinokitiol by incorporating it with the specific elements of the present invention, as amended.

Therefore, since Miyahara nowhere teaches or suggests the above-noted oral care benefits for hinokitiol in and of itself, much less teach combining hinokitiol with specific elements of the claimed invention for preventing, eliminating or suppressing plaque, gum disease and oral malodor, the compositions of the present invention, as amended, would not have been obvious over this reference.

Claims 1, 3-19, 21-27 and 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 3,164,524 to Fand, et al (Fand) or US Patent No. 4,945,087 to Talwar, et al (Talwar) in view of US Patent No. 5,939,050 to Iyer et al. (Iyer).

Applicants respectfully traverse this rejection.

Lyer relates to Antimicrobial compositions comprising at least two antimicrobial agents exhibit reduced MIC values relative to the MIC for the agents making up the combination when

measured alone. Lyer further teaches that the antimicrobial agents are selected from berberine, cedarwood oil, chloramphenicol, citral, citronella oil, cocamidopropyl dimethylglycine, Glycyrrhiza glabra extract, hinokitiol, juicy fruit basil oil, juniper berries oil, lemon basil oil, lemon oil, and Rosmarinus officinalis oil.

In contrast, the compositions of the present invention specifically require combining hinokitiol with an oral care effective amount of at least one essential oil in an oral carrier comprising about 20% to about 30% by weight of ethanol for preventing, eliminating or suppressing plaque, gum disease and oral malodor.

However, nowhere does Lyer teach such oral care benefits for hinokitiol apart from the cited antimicrobial agents, much less improving any such benefits of hinokitiol by incorporating it with the specifically claimed elements of the present invention.

Furthermore, the Examiner contends that, "Lyer also discloses hinokitiol has antimicrobial effects, which is its oral care benefit." Applicants respectfully submit, however, that mere antimicrobial effectiveness does not necessarily translate into an "oral care benefit". A compound's antimicrobial activity versus planktonic organisms (i.e., freely floating organisms) does not establish that compound's effectiveness versus the "biofilm" organisms found in the oral cavity (i.e., adherent, organized microbial communities). As noted by Michael L. Barnett in his article (copy enclosed) entitled The Role of Therapeutic Antimicrobial Mouthrinses in Clinical Practice,

> To appreciate fully the kind of information that can be obtained from various study designs, it is important to recognize that dental plaque is just one example of a category of adherent, organized microbial communities referred to as biofilms. *Bacteria in biofilms are different from those of the same species freely floating in a tube of culture medium, so-called "planktonic organisms."* Once bacteria adhere to a surface, they develop a phenotype that is altered from the one they had while floating freely. For example, they may start to produce an extracellular matrix and synthesize and release molecules that enable them to "communicate" with other bacteria within the mass (for

example, quorum-sensing molecules). Bacteria in biofilms usually are more resistant to antimicrobial agents than are planktonic organisms, as they are encased in an extracellular matrix that impedes access of the agent to the bacteria and because the phenotypic changes themselves may render the bacteria more resistant. *This is relevant to antimicrobial mouthrinse studies, as it suggests that assessments based on a mouthrinse's effect on planktonic organisms may not be indicative of the effectiveness of the mouthrinse against the plaque biofilm under actual-use conditions.* (Barnett ML. JADA 2003; 134:699-704) (Emphasis added).

Therefore, since Lyer nowhere teaches or suggests the above-noted oral care benefits for hinokitiol in and of itself, much less teach combining hinokitiol with specific elements of the claimed invention for preventing, eliminating or suppressing plaque, gum disease and oral malodor, the compositions of the present invention, as amended, would not have been obvious over this reference.

Nor is Lyer's inadequacy cured by combining it with either Fand or Talwar. Neither Fand nor Talwar even mention hinokitiol. Therefore, since neither Lyer, Fand, nor Talwar teaches or suggests the above-noted oral care benefits for hinokitiol in and of itself, much less teach combining hinokitiol with specific elements of the claimed invention for preventing, eliminating or suppressing plaque, gum disease and oral malodor, the compositions of the present invention, as amended, would not have been obvious over these references in combination.

Conclusion

Therefore, in light of the amendments and remarks made herein, it is respectfully submitted that the rejection under 35 USC § 103 has been overcome. Applicants respectfully submit that they have distinguished the cited art sufficiently to avoid the Examiner's rejection. Accordingly, reconsideration and allowance of Claims 1, 3-19, 21-27 and 31-33 are earnestly solicited.

Should the Examiner have any questions or comments concerning the above, the Examiner is respectfully invited to contact the undersigned attorney at the number listed below.

Date

March 21, 2008

Respectfully submitted,

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CLINICAL | PRACTICE

The role of therapeutic antimicrobial mouthrinses in clinical practice

Control of supragingival plaque and gingivitis

MICHAEL L. BARNETT, D.D.S.

Background. Although mechanical plaque control methods have the potential to maintain adequate levels of oral hygiene, clinical experience and population-based studies demonstrate that such methods are not being employed sufficiently by large numbers of the population. The need for additional help in controlling bacterial plaque provides the rationale for patients' using antimicrobial mouthrinses as adjuncts to their mechanical oral hygiene regimens.

Types of Studies Reviewed. The author presents an overview of the types of studies used to support the effectiveness of antiplaque and antigingivitis mouthrinses, ranging from laboratory studies to six-month clinical trials. He discusses plaque as an example of a biofilm and the implications of recent research on the nature of biofilms with respect to the nature of the evidence that can be used to demonstrate clinical effectiveness.

Conclusions. The safety and clinical effectiveness of antiplaque and antigingivitis antimicrobial mouthrinses are best determined using prospective, randomized clinical trials conducted in accordance with ADA guidelines.

Clinical Implications. The adjunctive use of antimicrobial mouthrinses can provide significant benefits to patients who cannot maintain adequate levels of plaque and gingivitis control through mechanical methods alone. Dentists should recommend products that have proven clinical activity as demonstrated using generally accepted safety and effectiveness criteria.

One of the pleasures that can be derived from practicing dentistry is the possibility of preventing much of the dental disease seen in patients by a low-tech, but effective, measure: the thorough daily control of dental plaque. In a classic experiment, Löe and colleagues[1] clearly demonstrated the role of plaque accumulation in the development of gingivitis. In their study, subjects with healthy gingiva ceased all oral hygiene procedures for three weeks, during which time plaque accumulation and signs of gingivitis were monitored. The results showed a clear temporal relationship between the accumulation and maturation of plaque and the onset of gingivitis. With the resumption of thorough plaque control at three weeks, the gingivitis quickly resolved, confirming the importance of plaque control to gingival health.

The adjunctive use of antimicrobial mouthrinses can provide significant benefits to patients who cannot maintain adequate levels of plaque and gingivitis control through mechanical methods alone.

Accordingly, a variety of implements have been marketed and used to facilitate the mechanical removal of plaque, including toothbrushes of varying shapes and configurations, dental floss, interdental brushes and toothpick holders.[2] It has been demonstrated in clinical studies that more frequent or intense episodes of instruction in plaque control can help control the onset or progression of periodontal diseases.[3-5] Experience in actual clinical practice, however, can be quite different. In fact, most patients often are not able to maintain adequate plaque control levels using mechanical methods alone, despite efforts to educate them about preventive procedures.

The experiences of individual practitioners are reflected in epidemiologic data from the United States and other countries that reveal that gingivitis was present in a majority of the people examined. For example, in the United States, 63 percent of dentate people examined in the Third National Health and Nutrition Examination Survey had gingivitis, as indicated by gingival bleeding on probing[6]; this prevalence likely is an underestimate of the true prevalence, since only two sites (the mesiobuccal and midbuccal) on each tooth in two randomly selected quadrants were assessed. In a Swedish study in which a random sample of 600 adults in six age groups from 20 to 70 years were examined in 1973, 1983 and 1993, researchers found that the levels of plaque accumulation and gingivitis in the 20-year-olds actually increased between 1983 and 1993.[7] A survey in Ireland revealed that gingivitis was present in 77 percent of people in the 16- to 24-year-old group and in 91 percent of the people in the 55- to 64-year-old group.[8] In a study conducted in the United Kingdom, researchers found visible plaque in 72 percent of adults; even when subjects cleaned their teeth immediately before their examinations, plaque still was seen on close to one-third of their teeth.[9] While these are just a few examples, a high prevalence of gingivitis and periodontal diseases can be seen in many countries worldwide.[10]

Bacteria in biofilms are different from those of the same species freely floating in a tube of culture medium.

Thus, from both clinical experience and population-based studies, it is clear that mechanical plaque control methods that in theory are able to maintain adequate levels of oral hygiene are in actuality not being employed sufficiently by large numbers of the population. The need for additional help in the control of bacterial plaque provides the rationale for the use of antimicrobial mouthrinses with clinically proven antiplaque and antigingivitis effectiveness as adjuncts to patients' mechanical oral hygiene regimens.[11]

EVIDENCE FOR EFFECTIVENESS

A variety of study types ranging from laboratory studies to long-term clinical trials have been used to support the effectiveness of antimicrobial mouthrinses. Given this range, it is necessary to consider what constitutes sufficient evidence to support clinical effectiveness of antiplaque and antigingivitis mouthrinse formulations. In this article, I consider the conclusions that can be drawn from the types of studies that have been conducted. I am not, however, presenting a rigorous evaluation of the literature that is typical of the evidence-based approach to clinical decision making that has become the cause célèbre of clinical practice.

To appreciate fully the kind of information that can be obtained from various study designs, it is important to recognize that dental plaque is just one example of a category of adherent, organized microbial communities referred to as biofilms.[12-16] Bacteria in biofilms are different from those of the same species freely floating in a tube of culture medium, so-called "planktonic organisms." Once bacteria adhere to a surface, they develop a phenotype that is altered from the one they had while floating freely. For example, they may start to produce an extracellular matrix and synthesize and release molecules that enable them to "communicate" with other bacteria within the mass (for example, quorum-sensing molecules). Bacteria in biofilms usually are more resistant to antimicrobial agents than are planktonic organisms, as they are encased in an extracellular matrix that impedes access of the agent to the bacteria and because the phenotypic changes themselves may render the bacteria more resistant.[17] This is relevant to antimicrobial mouthrinse studies, as it suggests that assessments based on a mouthrinse's effect on planktonic organisms may not be indicative of the effectiveness of the mouthrinse against the plaque biofilm under actual-use conditions.

Measures of antimicrobial effectiveness that are conducted on planktonic organisms include the kill kinetics assay, which assesses the percentage of organisms killed within a given period, and minimal inhibitory and bactericidal concentration determinations, which provide information about the lowest concentration of the mouthrinse exerting a growth inhibitory or outright killing effect. These measures provide important information about the antimicrobial spectrum and the potency of mouthrinse formulations. By themselves, however, they are not predictive of clinical effectiveness. When a quantity of mouthrinse is added to a tube containing planktonic organisms, the mouthrinse quickly mixes with the fluid culture medium and gains

access to the suspended microorganisms to exert its effect. It is not clear, however, that the mouthrinse will behave the same way when encountering the plaque biofilm, since it will have to penetrate the biofilm matrix to carry the active agents to the more densely packed bacteria within the brief period of a 30- or 60-second rinse. Thus, mouthrinses that might be effective against planktonic organisms may not be comparably effective against the same organisms contained within a biofilm.[18] Laboratory tests using biofilm models have been developed that help explain the differences among formulations, as well as mechanisms of action, and that may be more predictive of clinical effectiveness.[19-24]

There are a number of factors that might be important during the actual use of a mouthrinse that cannot be simulated in the laboratory and thus provide a requirement for clinical studies. They might include the contribution of substantivity to a product's effectiveness, interactions between salivary components and the active ingredient that might reduce its activity, and inhibitory interactions between a mouthrinse's active ingredients and the components of other oral hygiene products such as dentifrice.

There are a number of factors that might be important during the actual use of a mouthrinse that cannot be simulated in the laboratory.

CLINICAL STUDY DESIGNS

A wide range of clinical studies has been presented over the years in support of the effectiveness of therapeutic antimicrobial mouthrinses. At the least rigorous end of the spectrum are open trials, or so-called "pragmatic clinical trials," in which a test group of subjects uses a product according to label directions with full knowledge of what the product is. In these trials, there is no true control group, as the test group is compared with a group of people who have done nothing in addition to their usual oral hygiene procedures. Since it is known which product the test subjects used, such a design does little to minimize investigator bias and, in the absence of a true negative control group, does not allow for the factoring out of improvement resulting from a "Hawthorne effect," which will be discussed later. Trials using this protocol design have only limited value in determining the effectiveness of a given mouthrinse formulation.

There are four characteristics that are essential in assessing which types of clinical studies are the most credible:

- the trial should be controlled with a negative control group to which the test group can be compared;
- the trial should be blinded so that the examiner and all other personnel involved in evaluating data or laboratory specimens are not aware of which group a given subject is in;
- subjects meeting entry criteria should be assigned randomly to treatment and control groups;
- the trial should be prospective; that is, the protocol, entry criteria, random assignments and method of statistical analyses should be determined in advance of the actual treatment phase.

A number of blinded, randomized, prospective study designs have been used to demonstrate antimicrobial mouthrinse effectiveness. These include studies looking at salivary bacterial counts,[25,26] studies looking at plaque regrowth over a 24-hour[27] or four-day period[28-31] and studies using an experimental gingivitis model[32,33] based on Löe and colleagues' study.[1] These all have limitations that preclude their providing sufficient information about antiplaque and antigingivitis effectiveness for use in clinical decision making. Some investigators consider studies of subjects' salivary bacterial counts at various times after rinsing with test mouthrinses or placebos to be a surrogate for antiplaque activity. Such studies, however, do not assess the mouthrinse's activity against bacteria in biofilms and, of course, do not assess gingivitis. Four-day and 24-hour plaque regrowth studies may serve as a screening method or provide preliminary information about antiplaque activity, but they only evaluate short-term effects in the absence of mechanical oral hygiene and do not assess gingivitis. While experimental gingivitis studies look at both plaque and gingivitis, they are short-term (14-21 days) and, because they do not involve usual oral hygiene procedures, cannot reveal interactions that may occur between the mouthrinse and components in other products such as dentifrices. In addition, none of these study models allows for longer-term assessment of the oral flora or the occurrence of adverse effects under normal-use conditions.

BOX

GUIDELINES FOR EVALUATING CHEMOTHERAPEUTIC PRODUCTS FOR THE CONTROL OF SUPRAGINGIVAL PLAQUE AND GINGIVITIS.*

- Characteristics of the study population should represent typical product users
- Active product should be used in normal regimen and compared with a placebo control or, where applicable, an active control
- Crossover or parallel-designed studies are acceptable
- Studies should be a minimum of six months in duration
- Two studies conducted by independent investigators will be required
- Microbiological sampling should estimate plaque qualitatively to complement indexes that measure plaque quantitatively
- Plaque and gingivitis scoring and microbiological sampling should be conducted at baseline, six months and an intermediate period
- Microbiological profile should demonstrate that pathogenic or opportunistic microorganisms do not develop over the course of the study
- The toxicological profile of products should include carcinogenicity and mutagenicity assays in addition to generally recognized tests for drug safety

* Source: ADA Council on Dental Therapeutics.[34]

In the final analysis, the clinical effectiveness and safety of mouthrinses are best evaluated by using prospective, randomized clinical trials in which plaque and gingival indexes, the condition of the oral mucosal tissues and the composition of the oral flora are determined when the product is used according to the label directions and as an adjunct to usual mechanical oral hygiene procedures over a prolonged period. The ADA's Council on Dental Therapeutics (currently the ADA Council on Scientific Affairs) developed guidelines for the design of such clinical trials.[34] Pivotal studies included in product submissions for the ADA Seal of Acceptance are required to meet the requirements of these guidelines (Box). These guidelines also have been adopted, in some cases with modifications, by other professional and governmental organizations that evaluate antiplaque and antigingivitis products; these organizations include the U.S. Food and Drug Administration, or FDA; the Canadian Dental Association; and the British Dental Association.

Basically, these guidelines require that subjects entered into clinical trials be representative of a wide range of ages, both sexes and various ethnic groups, and that they have a specified level of plaque and gingivitis at the outset to indicate that their usual mechanical oral hygiene regimens are inadequate. Although the guidelines do not explicitly require that the subjects be randomly assigned to groups or that blinding is used, these features are implicit in the requirement for at least two groups, an active product and a placebo (or negative) control. Having a negative control helps minimize bias since the examiner will not know to which group any given subject has been assigned.

In addition, it usually is observed in these trials that all subjects will show some improvement, especially over the initial few months of the study. This generally is attributed to the so-called "Hawthorne effect," a tendency for subjects who know they are in a dental trial to unconsciously brush their teeth more thoroughly at first. This effect usually will diminish over time; if the mouthrinse is truly effective, subjects in this group will show significantly greater improvement than those in the negative control group during the latter phase of the study. Therefore, a comparison of the active group with the negative control group at six months will allow for an assessment of the true effectiveness of the mouthrinse in that it will factor out that portion of improvement resulting from the Hawthorne effect. There are several rationales for a six-month study duration: it is the "traditional" recall interval in dental practice, it provides sufficient time to determine if the product has any adverse effects such as tooth staining or mucosal irritation, and it provides enough time to determine whether the mouthrinse will have an adverse effect on the oral flora, such as allowing for the overgrowth of opportunistic pathogens.

Subsequent modifications to the guidelines[35] deal with issues of study design, such as making the need for randomization and blinding explicit; require a gingival bleeding component in the assessment of gingivitis; indicate methods for standardization of examiners; specify elements to be included in the statistical analyses; and establish a minimum acceptable effect level.

CLINICALLY PROVEN MOUTHRINSES

Active ingredients and marketed products containing these ingredients that are backed by published studies satisfying the ADA's guidelines are listed in the table.[38-45] Chlorhexidine and triclosan were approved by the FDA for use in oral care

TABLE

SUMMARY OF PUBLISHED SIX-MONTH PLAQUE/GINGIVITIS MOUTHRINSE CLINICAL STUDIES.

ACTIVE INGREDIENT	MARKETED PRODUCT	% PLAQUE REDUCTION*	% GINGIVITIS REDUCTION*	STUDY REFERENCE NO.
0.12 Percent Chlorhexidine	Peridex (Zila Pharmaceuticals; Phoenix)†	50.3-60.9	30.5-42.6	38-40
Fixed Combination of Essential Oils‡	Listerine Antiseptic (Pfizer, Morris Plains, N.J.)† Cool Mint Listerine (Pfizer)† FreshBurst Listerine (Pfizer)† Tartar Control Listerine (Pfizer)†	13.8-56.1	22.1-35.9	37-41
0.05 Percent Cetylpyridinium Chloride	Viadent (Colgate-Palmolive, New York)	28.2	24.0	42
0.03 Percent Triclosan	Plax (Colgate-Palmolive)§ Actibrush (Colgate-Palmolive)	24.0-29.1	16.9-23.0	43-45

* Compared with negative control at six months.
† This product has received the ADA Seal of Acceptance.
‡ Thymol 0.064 percent, eucalyptol 0.092 percent, methyl salicylate 0.060 percent and menthol 0.042 percent.
§ Plax with triclosan is marketed in countries outside of North America and is different from the Plax product marketed in North America, which is solely a cosmetic mouthwash.

products in the United States by means of the New Drug Application route. Triclosan-containing dentifrices were approved in the United States by the FDA. Triclosan-containing mouthrinses are not marketed in North America but are in other countries worldwide. The Plaque Products Subcommittee, an FDA advisory panel that reviewed antiplaque ingredients as part of a process intended to determine the safety and effectiveness of ingredients in nonprescription products with a significant marketing history, has recommended that two ingredients, the fixed combination of essential oils and cetylpyridinium chloride, be placed in Category 1 (safe and effective).

It is important to recognize that different formulations, or products, containing the same level of a given active ingredient may not necessarily have comparable clinical effectiveness. Mouthrinses essentially are topical delivery systems, and the way a product is formulated (that is, its inactive ingredients, or excipients) may affect factors such as the bioavailability of the active agent and biofilm penetrability, which can influence clinical activity. Therefore, appropriate studies should be conducted to verify that the level of clinical activity of a new or different mouthrinse formulation is comparable with that of a clinically tested product containing the same level of the active agent.

Although the primary endpoints in the six-month studies are supragingival plaque and gingival indexes, mouthrinses—because they are liquid delivery devices—can deliver active antimicrobial agents throughout the mouth in the course of rinsing. Therefore, it is likely that they also may reduce bacterial levels in sites that might serve as reservoirs for dental plaque bacteria, such as the dorsum of the tongue. In fact, studies have reported that use of an antiseptic mouthrinse results in significant reductions of tongue bacteria levels.[46,47]

CONCLUSIONS

Thus, the data indicate that the adjunctive use of antimicrobial mouthrinses can provide significant benefits to patients who cannot maintain adequate levels of plaque and gingivitis control through mechanical methods alone. When recommending such products, dentists need to ensure that their patients understand that using a mouthrinse is not a substitute for mechanical oral hygiene procedures and that daily compliance

with label directions and their professional recommendations are essential to the most successful outcome. ■

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